(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 0 655 451 B1

(12) **EUROPEAN PATENT SPECIFICATION**

(45) Date of publication and mention of the grant of the patent:
20.06.2001 Bulletin 2001/25

(21) Application number: **94118734.6**

(22) Date of filing: **29.11.1994**

(51) Int Cl.[7]: **C07D 487/04**, C07D 471/06, A61K 31/55, A61K 31/435 // (C07D487/04, 223:00, 209:00), (C07D471/06, 221:00, 209:00)

(54) **Tetracyclic condensed heterocyclic compounds for the treatment of senile dementia**

Tetracyclische kondensierte heterocyclische Verbindungen zur Behandlung von seniler Demenz

Composés hétérocycliques condensés tétracycliques, pour le traitement de la démence sénile

(84) Designated Contracting States:
AT BE CH DE DK ES FR GB GR IE IT LI LU NL PT SE

(30) Priority: **30.11.1993 JP 29979993**
25.03.1994 JP 5598494

(43) Date of publication of application:
31.05.1995 Bulletin 1995/22

(73) Proprietor: **TAKEDA CHEMICAL INDUSTRIES, LTD.**
Chuo-ku, Osaka 541 (JP)

(72) Inventors:
- **Goto, Giichi**
  Toyono-gun, Osaka 563-01 (JP)
- **Ishihara, Yuji**
  Itami, Hyogo 664 (JP)
- **Miyamoto, Masaomi**
  Takarazuka, Hyogo 665 (JP)

(74) Representative:
von Kreisler, Alek, Dipl.-Chem. et al
Patentanwälte,
von Kreisler-Selting-Werner,
Bahnhofsvorplatz 1 (Deichmannhaus)
50667 Köln (DE)

(56) References cited:
EP-A- 0 441 517
EP-A- 0 487 071
EP-A- 0 607 864
WO-A-93/07140
JP-A- 4 013 626
US-A- 3 403 156
US-A- 4 192 874

- **ARCHIVES INTERNATIONALES DE PHARMACODYNAMIE ET DE THERAPIE, vol.257, 1982, GHENT, BE pages 188 - 199 J.D. SWEATT ET AL. 'Benzo [b]-promazines, chlorpromazine free radical and analino-N,N-dimethylpropylamine analogs influence rat striatal Da-adenylate cyclase and calmodulin-phosphodiesterase'**
- **ANNALES PHARMACEUTIQUES FRANCAISES, vol.38, no.6, 1980, PARIS FR pages 537 - 544 M. LEBOEUF ET AL. 'Alcaloïdes du Monimia rotundifolia Pet.-Th.'**
- **JOURNAL OF MEDICINAL CHEMISTRY, vol.23, 1980, WASHINGTON US pages 1380 - 1386 E. J. GLAMKOWSKI ET AL. '7-(Aminoacyl) and 7-(aminoalkyl) derivatives of 1,2,6,7-tetr ahydrindolo[1,7-ab][1,5]benzodiazepines as potential antidepressant agents'**
- **CHEMICAL ABSTRACTS, vol. 92, no. 21, 1980, Columbus, Ohio, US; abstract no. 181036j, M. HIROBE ET AL. 'N-Acyl-10,11-dihydrdibenz[b,f]azepine 10,11-epoxides' page 641 ; & JP-A-79 145 690 (KOWA) 14 November 1979**
- **CHEMICAL ABSTRACTS, vol. 77, no. 11, 1972, Columbus, Ohio, US; abstract no. 69985g, G.N. ARTEMENKO ET AL. 'Pharmacological activity spectra of some azepino- and benzoxepinoindole derivatives' page 11 ; & FARMAKOL. TOKSIKOL (MOSCOW) 1972, 35 (3), 274-80**
- **CHEMICAL ABSTRACTS, vol. 76, no. 7, 1972, Columbus, Ohio, US; abstract no. 34140e, L.A. AKSANOVA ET AL. 'Indole derivatives. XXXVI. Synthesis and pharmacological study of some benzoxepinoindole derivatives' page 310 ; & KHIM.-FARM. ZH. 1971, 5(11), 3-5**

EP 0 655 451 B1

(Cont. next page)

- **JOURNAL OF THE AMERICAN PHARMACEUTICAL ASSOCIATION. SCIENTIFIC EDITION, vol.60, no.8, 1971, WASHINGTON US pages 1236 - 1238 N.J. DOORENBOS ET AL. 'Derivatives of 17a-aza-D-homo-5-androsten-3beta-ol'**
- **CHEMICAL ABSTRACTS, vol. 70, no. 25, 1969, Columbus, Ohio, US; abstract no. 115036d, M.N. SHARKOVA ET AL. 'Indole derivatives. XXVIV. Synthesis of some new polycondensed indole-systems' page 335 ; & KHIM. GETEROTSIKL. SOEDIN. 1969, (1), 88-90**

Remarks:

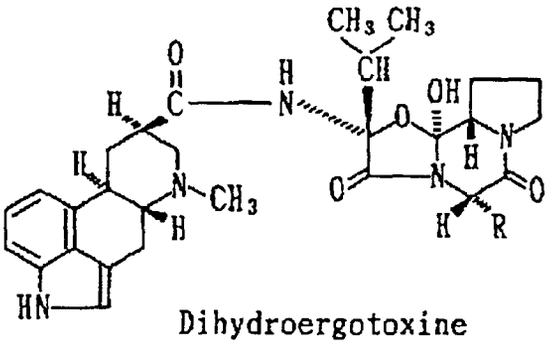
The file contains technical information submitted after the application was filed and not included in this specification

Description

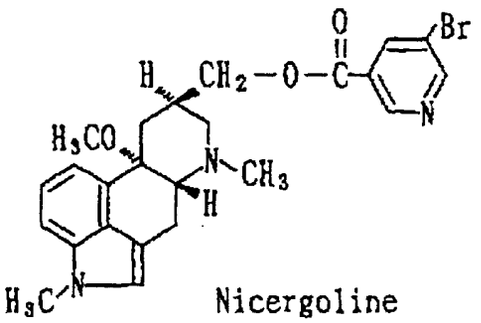
[0001] This invention relates to a medicine and more particularly to a cholinesterase inhibitor composition, inter alia a therapeutic and/or prophylactic drug for senile dementia and symptoms of senile dementia in Altzheimer's and other diseases, a novel tetracyclic fused heterocyclic derivative or a salt thereof for use as its active ingredient, and processes for its production.

[0002] With an increasing mean age of the population, a variety of compounds having therapeutic and/or prophylactic effects on senile dementia have so far been proposed. Among them, tacrine (THA) and physostigmine, both of which are inhibitors of cholinesterase, have been found to have anti-senile dementia activity [cf. International Journal of Clinical Pharmacology, Therapy and Toxicology, Vol. 29, No. 1, p. 23-37, 1991, etc.]. However, severe hepatic impairment is often associated with THA, while physostigmine has the drawback of a short duration of action and a high toxic potential.

[0003] Meanwhile, naturally-occurring ergot alkaloids are known to be tetracyclic fused heterocyclic compounds having an (iso)indole ring. Particularly as to dihydroergotoxine and nicergoline, their potential utility as therapeutic agents for senile dementia has been explored (Z. REHACEK and P. SAJDL., "Bioactive Molecules. vol. 12 : ERGOT ALKALOIDS", ELSVIER, 1990, p. 74).



Dihydroergotoxine

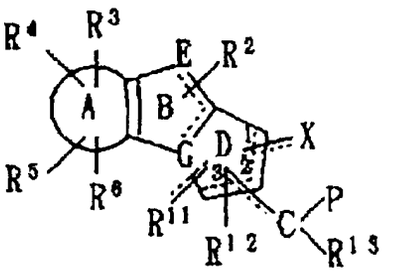


Nicergoline

[0004] However, there is no disclosure, nor a suggestion, in the literature about cholinesterase inhibitory activity in these compounds.

[0005] Meanwhile, as synthetic versions, a variety of bicyclic or tricyclic fused heterocyclic compounds each having a (dihydro)indole ring have been proposed as inhibitors of cholinesterase (JP-A-4(1992)-234845, JP-A-5(1993)-140149, WO9307140 and 9312085, and EP560235 and 562832).

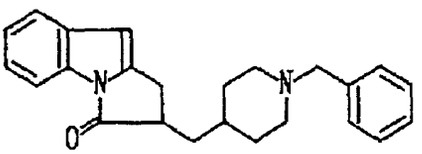
[0006] JP-A-4(1992)-234845 discloses a tricyclic cyclicamine compound of the formula



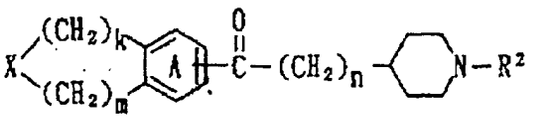
[1]

[wherein P represents an N-substituted piperidin-1-yl (N-substituted piperazin-1-yl)methyl group or the like; G represents carbon or nitrogen; E represents carbon, nitrogen, oxygen or sulfur; ring A represents an aromatic ring such as benzene, pyridine, thiophene or the like] and a pharmaceutical composition comprising the same compound as an active ingredient.

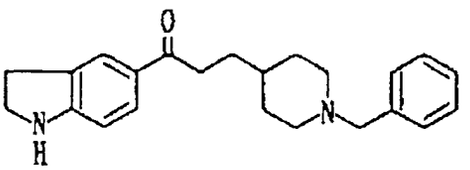
[0007] It is described there that compounds of formula [I] having the above ABD ring system, which includes such species as 1H-pyrrolo[1,2-a]indol-1-one, cyclopento[d]indol-3-one, cyclopento[b](benzo[b]thieno)-1-one, 1H-pyrrolo [1,2-a](6-azaindol)-1-one, pyrrolo[1,2-a](thieno[2,3-b]pyrrol)-1-one, etc., have cholinesterase inhibitory activity and a pharmaceutical composition comprising any of the compounds as an active ingredient is instrumental for augmentation of memory in patients with dementia or Artzheimer's disease. Specifically, the following compound has been described, among others.



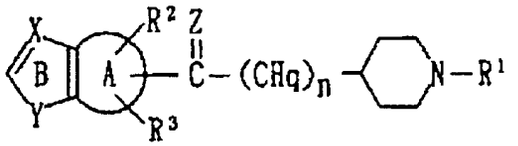
[0008] JP-A5(1993)-140149 discloses a fused heterocyclic derivative of the formula



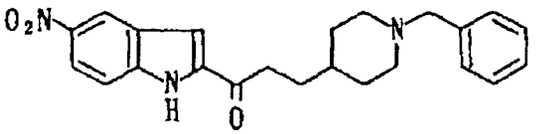
wherein X represents R^1-N< (R^1 represents a hydrogen atom, a hydrocarbon group which may be substituted or an acyl group which may be substituted), an oxygen atom or a sulfur atom; R^2 represents a hydrogen atom or a hydrocarbon group which may be substituted; ring A represents a benzene ring which may be substituted; k represents a whole number of 0-3; m represents a whole number of 1-8; n represents a whole number of 1-6, or a salt thereof. Specifically, the following compound, among others, has been disclosed.



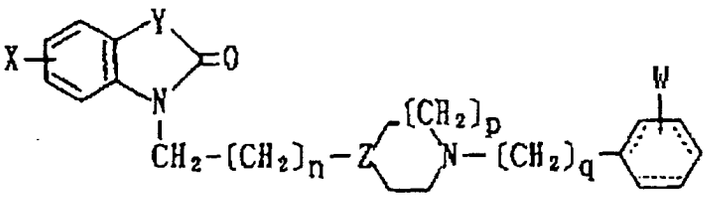
[0009] WO9307140 discloses a compound of the formula



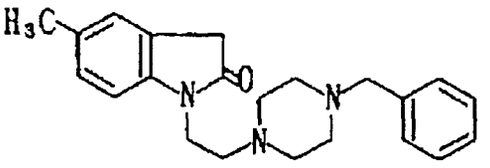
[wherein ring A represents benzo, thieno, pyrido, pyrazino, pyrimido, furano, seleno, pyrrolo, thiazolo or imidazolo; R^1 represents phenyl, phenyl(C_1-C_6)alkyl, cinnamyl or heteroarylmethyl (where the heteroaryl represents imidazolo, thiazolo, thieno, pyrido or isoxazolo); said phenyl and heteroaryl each may have 1-2 substituent groups selected from among (C_1-C_6)alkyl, (C_1-C_6)alkoxy and halogen; R^2 and R^3 each represents hydrogen, (C_1-C_6)alkoxy or (C_1-C_6)alkyl [where the alkyl may be substituted by 1-3 substituent groups selected from fluoro, benzyloxy, hydroxy, phenyl, benzyl, halogen, nitro, cyano, CO_2R^4, $CONHR^4$, NR^4R^5, NR^4COR^5 and $SOpCH_2Ph$ (where p is equal to 0, 1 or 2) or R^2 and R^3 may, taken together with the adjacent carbon atom, represent a 5- or 6-membered ring (the ring constituent atoms are selected from among carbon, nitrogen and oxygen; e.g. methylenedioxy, ethylenedioxy, or a lactam ring); R^4 and R^5 independently represent a hydrogen atom or a (C_1-C_6)alkyl group; R^4 and R^5 of said NR^4R^5 may, taken together with the adjacent nitrogen atom, form a 4- through 8-membered ring containing at least one nitrogen atom (the other ring constituent atoms are selected from carbon, oxygen and nitrogen); R^4 and R^5 of said NR^4COR^5 may, taken together with the adjacent nitrogen and carbon atoms, form a 4- through 8-membered lactam ring; X represents nitrogen or CH; Y represents oxygen, sulfur or NR^6; R^6 represents hydrogen, (C_1-C_6)alkyl, CO(C_1-C_6)alkyl or SO_2-phenyl [the phenyl may have 1-5 substituent groups independently selected from (C_1-C_4)alkyl groups; n represents a whole number of 1 through 4; q in each occurrence independently represents 1 or 2; Z represents oxygen or sulfur]. Specifically, the following compound, among others, has been disclosed.



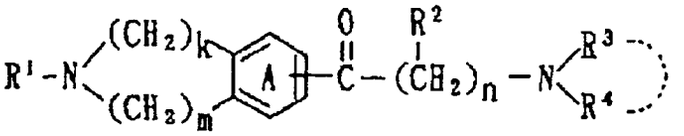
[0010] WO9312085 discloses a compound of the formula



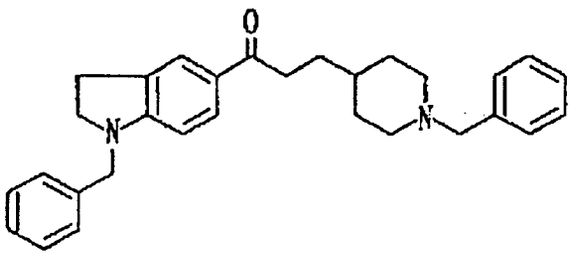
wherein X represents 1 or more substituent groups independently selected from hydrogen, lower alkyl, aryl, aryloxy, cyano, lower alkoxy, halogen, hydroxy, nitro, trifluoromethyl, alkylsulfonamido, NHCOR (where R represents lower alkyl or aryl), NR_1R_2 (where R_1 and R_2 independently represents a hydrogen atom or a lower alkyl group or combindly form a ring), and CO_2R (where R represents lower alkyl, cycloalkyl, cycloalkenyl or bicycloalkyl, which may be further substituted by lower alkyl); Y represents CO or CR_3R_4 (R_3 and R_4 independently represents hydrogen, lower alkyl or lower alkoxy or jointly form a cycloacetal group); Z represents nitrogen or CH. Specifically, the following compound, among others, has been described.



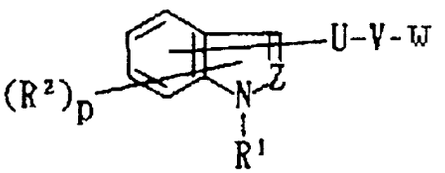
[0011] EP560235 discloses a fused heterocyclic ketone derivative of the formula



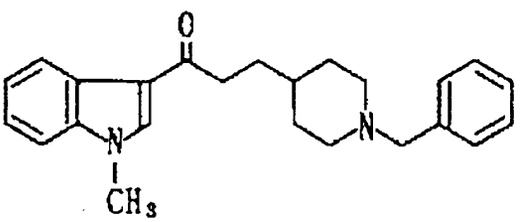
wherein R^1 represents a hydrogen atom, a hydrocarbon group which may be substituted or an acyl group which may be substituted; ring A represents a benzene ring which may be substituted; n represents a whole number of 1 through 10; R^2, R^3 and R^4 are the same or different and each represents a hydrogen atom or a hydrocarbon group which may be substituted; or R^3 and R^4 may, taken together with the adjacent nitrogen atom, form a heterocyclic group; R^2 may be different with different repeats of n; k represents a whole number of 0 through 3; m represents a whole number of 1 through 8; provided, however, that where k=0 and m=2, n>1, or a salt thereof. Specifically, the following compound, among others, has been disclosed.



[0012] EP562832 discloses a compound of the formula



wherein R^1 and R^2 each represents a hydrogen atom or an organic group; p represents 0, 1, 2 or 3; U represents -CO- or -CH(OR^3)- (where R^3 represents a hydrogen atom or a hydroxy-protecting group); V represents an aliphatic hydrocarbon group which may be unsaturated; W represents a nitrogen-containing group. Specifically, the following compound, among others, has been described.



[0013] Further prior art documents are:

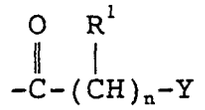
US-A-4 192 874;
J. Med. Chem., **23**, 1380, (1980);

US-A-3 403 156;
Chem. Abstr. 77: 69985g;
Chem. Abstr. 76: 34140e;
Chem. Abstr. 92: 181036j;
Ann. Pharm. Fr., **38**, 537, (1980);
Arch. Int. Pharm., **257**, 188, (1982);
Chem. Abstr. 70: 115036d;
J. Pharm. Sci., **60**, 1236, (1971);
JP-A-4 013 626 (abstract), 1992; and EP-A-0 607 864.

[0014] However, none of these official papers mention or even suggest a tetracyclic fused heterocyclic group of a type as defined in claim 1.

[0015] In the face of an increasing incidence of senile dementia, there is a strong demand for an anti-senile dementia agent which is longer in the duration of action and lower in the toxicological risk level than the hitherto-known compounds having therapeutic or prophylactic effects on senile dementia.

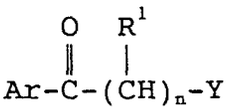
[0016] Under the circumstances, the inventors of this invention explored into the biological and pharmacological activities of various heterocyclic compounds including novel compounds and found surprisingly that a novel class of compounds having a unique chemical structure representing a direct combination between a tetracyclic fused heterocycle and a group of the formula



wherein the symbols have the same meanings as defined below] has excellent cholinesterase inhibitory activity and monoamine reuptake inhibitory activity on account of said unique chemical structure and is, therefore, of value as a therapeutic and/or prophylactic agent for senile dementia. They have accordingly brought this invention into being.

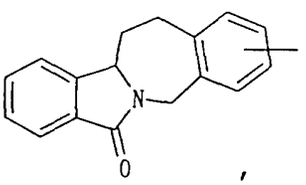
[0017] Thus, this invention relates to:

(1) a compound of the formula

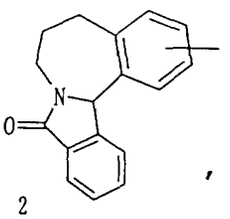


(I)

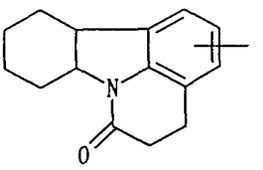
wherein Ar represents a group of the formula:



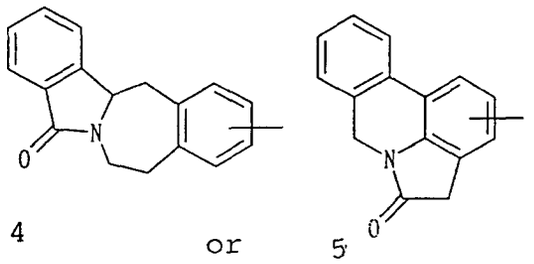
1



2



3



4 or 5 ;

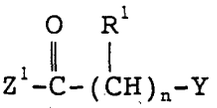
n represents an integer of 1 to 10;
R1 represents a hydrogen atom; and
Y represents a 1- or 4-piperidinyl or 1-piperazinyl group substituted by a benzyl which may be substituted by halogen, C_{1-4} alkyl, C_{1-4} alkoxy, hydroxy, nitro, amino or cyano; or a salt thereof.

(2) A process for producing the compound (I) which comprises

(i) reacting a compound of the formula

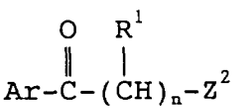
Ar-H (II)

wherein Ar has the same meaning as defined above, or a salt thereof with a compound of the formula



(III)

wherein R^1, Y and n have the same meanings as defined above; Z^1 represents a leaving group, or a salt thereof, or
ii) reacting a compound of the formula



(IV)

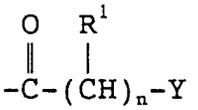
or a salt thereof with a compound of the formula

Z^3-Y

wherein Z^2 and Z^3 represent leaving groups and Y has the same meaning as defined in claim 1 or a salt thereof.

(3) A cholinesterase inhibitor composition comprising the compound (I).
(4) A therapeutic and/or prophylactic agent for senile dementia which contains the compound (I).

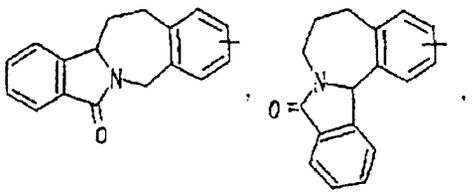
[0018] The compound (I) or its salt, of this invention is a novel compound having a characteristic chemical structure comprising a tetracyclic fused heterocycle substituted by a substituent group of the formula

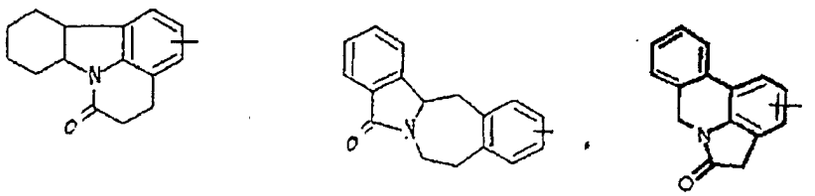


and, because of this characteristic structure, exhibits potent anti-senile dementia activity.

[0019] Referring to the above formula, n represents a whole number of 1 through 10.

[0020] Ar is one of the following groups.



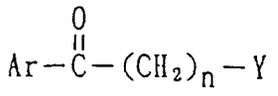


[0021] Y is 1- or 4-piperidinyl and 1-piperazinyl group substituted by benzyl which may be substituted by halogen (e.g. fluoro, chloro), C_{1-4} alkyl (e.g. methyl, ethyl), C_{1-4} alkoxy (e.g. methoxy), hydroxy, nitro, amino or cyano.

[0022] Preferably n stands for a whole number of 2-6, especially 2.

[0023] Specifically, the following compounds meeting the definition of compound (I) and their salts are preferred.

Table 1



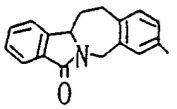
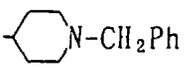
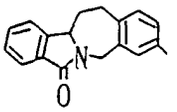
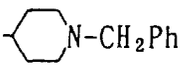
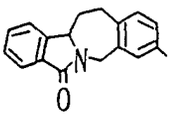
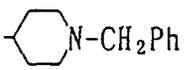
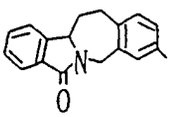
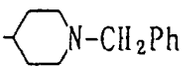
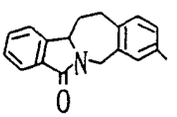
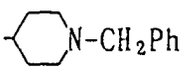
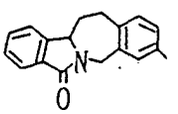
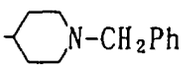
No.	Ar	n	Y
1		1	
2		2	
3		3	
4		4	
5		5	
6		6	

Table 2

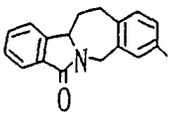
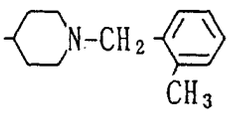
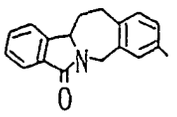
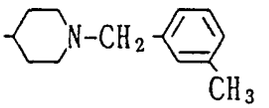
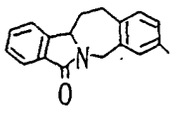
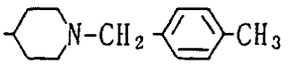
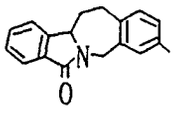
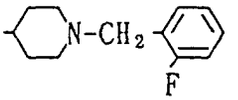
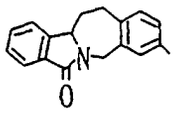
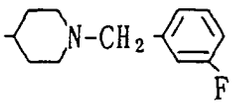
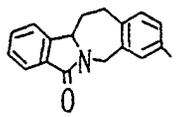
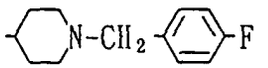
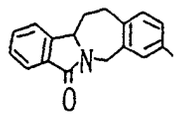
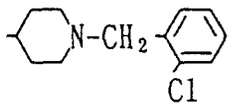
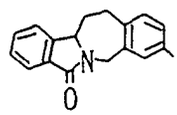
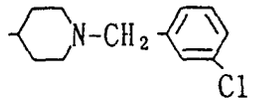
No.	Ar	n	Y
7		2	
8		2	
9		2	
10		2	
11		2	
12		2	
13		2	
14		2	

Table 3

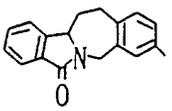
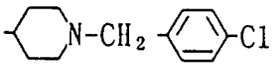
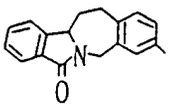
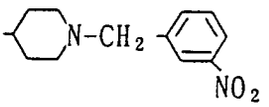
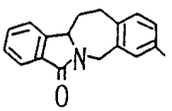
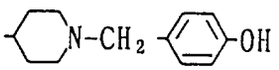
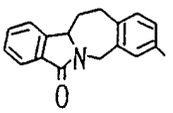
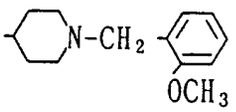
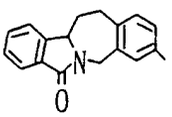
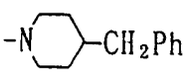
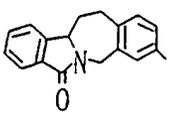
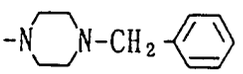
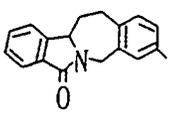
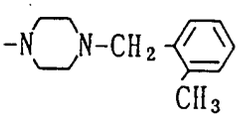
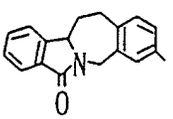
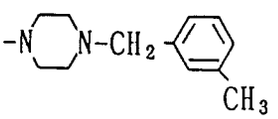
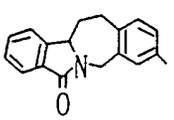
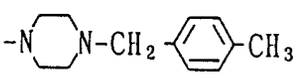
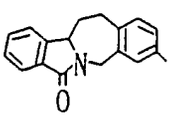
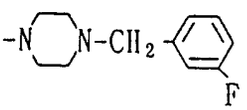
No.	Ar	n	Y
15		2	
16		2	
17		2	
18		2	
19		2	
20		2	
21		2	
22		2	
23		2	
24		2	

Table 4

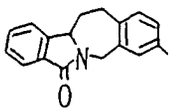
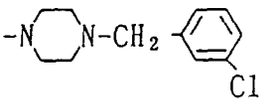
No.	Ar	n	Y
25		2	

Table 5

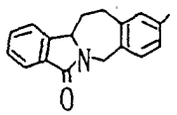
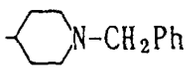
No.	Ar	n	Y
26		2	

Table 6

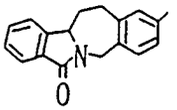
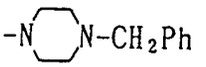
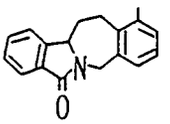
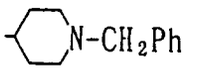
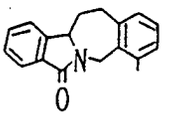
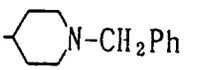
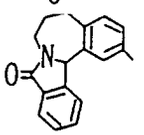
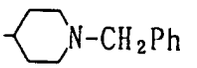
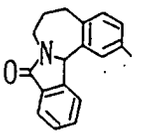
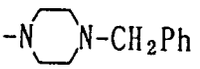
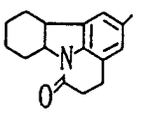
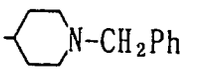
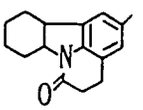
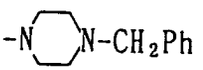
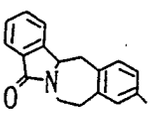
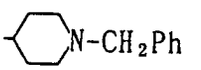
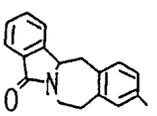
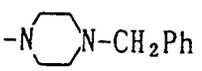
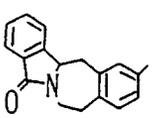
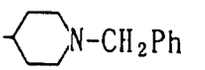
No.	Ar	n	Y
27		2	
28		2	
29		2	
30		2	
31		2	
32		2	
33		2	
34		2	
35		2	
36		2	

Table 7

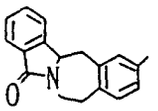
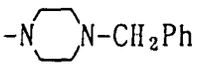
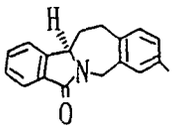
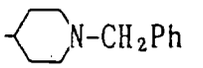
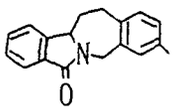
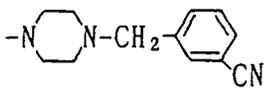
No.	Ar	n	Y
37		2	

Table 8

No.	Ar	n	Y
38		2	
39		2	

[0024] In the above table, Ph stands for phenyl.

[0025] The salt of compound (I) according to this invention is preferably a physiologically acceptable acid addition salt. Among such salts are salts with inorganic acids (e.g. hydrochloric acid, phosphoric acid, hydrobromic acid, sulfuric acid) and salts with organic acids (e.g. acetic acid, formic acid, propionic acid, fumaric acid, maleic acid, succinic acid, tartaric acid, citric acid, malic acid, oxalic acid, benzoic acid, methanesulfonic acid, benzenesulfonic acid).

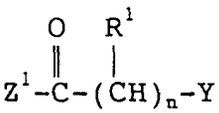
[0026] The method for production of compound (I) or a salt thereof is now described.

[0027] While the following production processes apply to both the production of compound (I) and that of its salt, reference is made only to compound (I) in the following description.

[0028] The compound (I) can be produced by reacting a compound of the formula

Ar-H (II)

wherein Ar has the same meaning as defined hereinbefore, or a salt thereof with a compound of the formula

 (III)

wherein Z^1 represents a leaving group; the other symbols have the same meanings as defined hereinbefore, or a salt thereof.

[0029] The leaving group Z^1 includes halogen (e.g. chloro, bromo, iodo), C_{1-6} alkylsulfonyloxy (e.g. methanesulfonyloxy, ethanesulfonyloxy) and C_{6-10} arylsulfonyloxy (e.g. benzenesulfonyloxy, p-toluenesulfonyloxy), among others, Particularly preferred is halogen (e.g. chloro).

[0030] The compound (II) or a salt thereof can be produced by the per se known processes or any processes analogous thereto. Thus, for example, the processes described in J. Chem. Soc., Perkin Trans 1 , 1547 (1979), Chem. Pharm. Bull., 38, 3024 (1990), J. Org. Chem., 37, 3755 (1972), J. Med. Chem., 14, 448 (1971), JP-A-5(1993)-502659, etc. and modifications of such processes can be mentioned.

[0031] The compound (III) or a salt thereof can be produced by the per se known processes and processes analogous

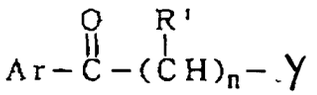
thereto. For example, the processes described in Chem. Pharm. Bull. 34, 3747-3761 (1986), and EP-A-0, 378,207 among others, can be utilized.

[0032] The salt of compound (II) or of compound (III) includes salts with inorganic acids (e.g. hydrochloric acid, phosphoric acid, hydrobromic acid, surfuric acid) and salts with organic acids (e.g. acetic acid, formic acid, propionic acid, fumaric acid, maleic acid, succinic acid, tartaric acid, citric acid, malic acid, oxalic acid, benzoic acid, methanesulfonic acid, benzenesulfonic acid).

[0033] The reaction of compound (III) or a salt thereof with compound (II) or a salt thereof can be carried out by causing said compound (III) or salt and said compound (II) or salt to interact in the absence of a solvent or, if necessary, in a solvent. The solvent can be any solvent for chemical reaction unless it does interfere with the intended reaction and, thus, includes various organic solvents such as hydrocarbons (e.g. pentane, hexane, benzene, toluene, nitrobenzene), halogenated hydrocarbons (e.g. dichloromethane, chloroform, 1,2-dichloroethane, carbon tetrachloride), ethers (e.g. ethyl ether, tetrahydrofuran, dioxane, dimethoxyethane), nitroalkanes (e.g. nitromethane, propionitrile), carbon disulfide and so on. Particularly preferred are dichloromethane, 1,2-dichloroethane, nitrobenzene and carbon disulfide. The amount of the solvent is generally 0.5-100 ml and preferably 5-20 ml per millimole of compound (III) or a salt thereof. The reaction temperature is generally about -30°C through 150°C and preferably about 20°C through 100°C. The reaction time is generally 0.5-72 hours and preferably about 1-16 hours.

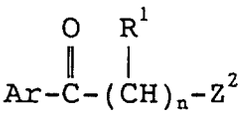
[0034] This reaction can be carried out using a Lewis acid for promotion of the reaction. The Lewis acid includes aluminum chloride, aluminum bromide, zinc chloride, titanium chloride, tin (IV) chloride, boron trifluoride, iron (II) chloride, iron (III) chloride, antimony (V) pentachloride, bismuth (III) chloride, mercury (II) chloride, hydrogen fluoride, sulfuric acid, polyphosphoric acid and so on. Particularly preferred is aluminum chlorlde. The proportion of the Lewis acid based on each mole of compound (III) or a salt thereof is generally 1-10 moles and preferably 2-10 moles. The amount of compound (II) or a salt thereof per mole of compound (III) or a salt thereof is generally about 1-20 moles and preferably about 1-5 moles.

[0035] The compound of the formula



(VI)

wherein all symbols have the same meanings as defined hereinbefore, or a salt thereof can be produced by reacting a compound of the formula



(IV)

wherein all symbols have the same meanings as defined hereinbefore, or a salt thereof with a compound of the formula

$$Z^3\text{-}Y \qquad (V)$$

wherein all symbols have the same meanings as defined hereinbefore, or a salt thereof.

[0036] Z^2 and Z^3 represent groups which react with each other and leave together.

[0037] The leaving group Z^2 includes halogen (e.g. chloro, bromo, iodo), $C_{1\text{-}6}$ alkylsulfonyloxy (e.g. methanesulfonyloxy, ethanesulfonyloxy), $C_{6\text{-}10}$ arylsulfonyloxy (e.g. benzenesulfonyloxy, p-toluenesulfonyloxy) and so on. Particularly preferred is halogen. More specifically, such species of halogen as chloro, bromo, etc. are preferred.

[0038] The leaving group Z^3 which leaves together with Z^2 includes hydrogen, trialkylsilyl (e.g. trimethylsilyl, triethylsilyl, t-butyldimethylsilyl) and metal atoms (e.g. sodium, potassium, lithium). Particularly useful is hydrogen.

[0039] The salt of compound (VI) may be similar to the salt of compound (I).

[0040] The salt of compound (IV) and of compound (V) includes salts with inorganic acids (e.g. hydrochloric acid, phosphoric acid, hydrobromic acid, sulfuric acid) and salts with organic acids (e.g. acetic acid, formic acid, propionic acid, fumaric acid, maleic acid, succinic acid, tartaric acid, citric acid, malic acid, oxalic acid, benzoic acid, methanesul-

fonic acid, benzensulfonic acid), among others.

[0041] The amount of compound (V) or a salt thereof for use in this reaction is generally 1.0-50.0 molar equivalents, preferably 1.0-10.0 molar equivalents, based on each mole of compound (IV) or a salt thereof. This reaction can be carried out under cooling through heating (0°C - 120°C). The reaction time is generally 10 minutes - 48 hours and preferably 2-16 hours.

[0042] While this reaction can be carried out in the absence of a solvent, it can be conducted in a solvent where necessary. The solvent that can be used for this purpose includes any solvents that do not hinder the progress of the reaction, thus including lower alcohols such as methanol, ethanol, propanol, isopropyl alcohol, n-butanol, t-butanol, etc., halogenated hydrocarbons such as dichloromethane, 1,2-dichloroethane, etc., ethers such as dioxane, diethyl ether, tetrahydrofuran, etc., aromatic hydrocarbons such as toluene, benzene, xylene, etc., amides such as dimethylformamide, dimethylacetamide, hexamethylphosphonotriamide, etc., and esters such as ethyl acetate, butyl acetate, etc., among others. The proportion of the solvent based on each millimole of compound (IV-a) or a salt thereof is generally 0.5-100 ml and preferably 5-20 ml.

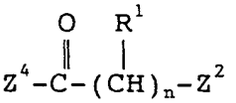
[0043] Where necessary this reaction can be carried out in the presence of a base. The base that can be used includes inorganic bases such as sodium carbonate, potassium carbonate, lithium carbonate, sodium hydroxide, potassium hydroxide, sodium methoxide, sodium ethoxide, sodium hydride, etc. and organic bases such as pyridine, 4-dimethylaminopyridine, triethylamine and so on. The amount of the base with respect to compound (V) or a salt thereof is generally equimolar to a stoichiometric excess and preferably 1.0-5.0 molar equivalents.

[0044] To accelerate its progress, this reaction can be carried out in the presence of an iodide (e.g. sodium iodide, potassium iodide, lithium iodide) or the like. The amount of the iodide with respect to compound (IV) or a salt thereof is generally 1-5 molar equivalents and preferably 1.0-1.5 equivalents.

[0045] The starting compound (IV) or a salt thereof can be produced by, for example, reacting a compound of the formula

Ar-H (II)

wherein Ar has the same meaning as defined hereinbefore, or a salt thereof with a compound of the formula



(VIII)

wherein Z^4 represents a leaving group; the other symbols have the same meanings as defined hereinbefore.

[0046] The leaving group Z^4 includes halogen (e.g. chloro, bromo, iodo), C_{1-6} alkylsulfonyloxy (e.g. methanesulfonyloxy, ethanesulfonyloxy), C_{6-10} arylsulfonyloxy (e.g. benzenesulfonyloxy, p-toluene-sulfonyloxy) and so on. Particularly preferred is halogen (e.g. chloro).

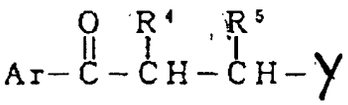
[0047] The compound (VIII) can be produced by the per se known processes or any processes analogous thereto.

[0048] The reaction of compound (II) or a salt thereof with compound (III) can be carried out under the same conditions as the reaction of compound (II) or a salt thereof with compound (III) or a salt thereof.

[0049] The compound (IV) or a salt thereof thus produced can be isolated and purified by the conventional procedures such as concentration, pH adjustment, redistribution, solvent extraction, fractional distillation, distillation, crystallization, recrystallization, chromatography, etc. but the reaction mixture may be submitted to the next reaction without isolation of the compound or a salt thereof.

[0050] The starting compound (V) or a salt thereof can be produced by the per se known processes or any processes analogous thereto.

[0051] Among species of compound (I), a compound wherein n is equal to 2, that is to say a compound of the formula

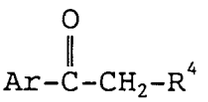


(IX)

wherein R^4 and R^5 each represents a hydrogen atom,

and the other symbols have the same meanings as defined hereinbefore, or a salt thereof can also be produced

by, for example, reacting a compound of the formula



(X)

wherein all symbols have the same meanings as defined hereinbefore, or a salt thereof with a compound of the formula

$$R^5\text{-CHO} \qquad \text{(XI)}$$

wherein R^5 has the same meaning as defined hereinbefore and a compound of the formula

$$Z^3\text{-Y} \qquad \text{(V)}$$

wherein all symbols have the same meanings as defined hereinbefore or a salt thereof.

[0052] The salt of compound (IX) may be similar to the salt of compound (I).

[0053] The salt of compound (X) includes salts with inorganic acids (e.g. hydrochloric acid, phosphoric acid, hydrobromic acid, sulfuric acid) and salts with organic acids (e.g. acetic acid, formic acid, propionic acid, fumaric acid, maleic acid, succinic acid, tartaric acid, citric acid, malic acid, oxalic acid, benzoic acid, methanesulfonic acid, benzenesulfonic acid), among others.

[0054] This reaction can be carried out in the manner of Mannich reaction as described in Organic Reactions Vol. 1, p. 303-341 and other literature. Thus, for example, compound (IX) or a salt thereof can be produced by using generally 0.9-10 equivalents, preferably 1.0-3.0 equivalents, of compound (XI) and compound (V) or a salt thereof with respect to each mole of compound (X) or a salt thereof. This reaction can be conducted generally at ambient temperature or under heating (10-150°C) and preferably at a temperature of 80-120°C. The reaction time is generally 1-48 hours and preferably 2-24 hours. This reaction is generally conducted in the absence of a solvent but can be conducted in a solvent. The solvent that can be used includes any and all solvents that can be used generally in Mannich reaction provided they do not interfere with progress of the reaction and includes alcoholic solvents such as ethanol. The proportion of the solvent with respect to each millimole of compound (X) or a salt thereof is generally 0.5-200 ml and preferably 5-40 ml. If desired, this reaction can be conducted in the presence of an inorganic acid such as hydrochloric acid. The amount of the acid is a catalytic amount with respect to compound (IV) or a salt thereof [0.001-0.05 equivalent per equivalent of compound (X)]. However, when the reactant compound (V) or (X) is not a salt, it is preferable to employ the acid in an additional amount necessary for the formation of a salt.

[0055] The compound (X) or a salt thereof can be produced by reacting compound (II) or a salt thereof with a compound of the formula

$$Z^5\text{-CO-CH}_2\text{-R}^4 \qquad \text{(XII)}$$

wherein Z^5 represents a leaving group; R^4 has the same meaning as defined hereinbefore. This reaction can be carried out under the same conditions as the above-mentioned reaction between compound (II) or a salt thereof and compound (VIII).

[0056] The compound (XI) can be produced by the per se known processes or any processes analogous thereto.

[0057] In the above respective reactions, where the starting compound has an amino or hydroxyl group as a substituent, it may be protected with a protective group which is generally utilized in peptide chemistry, for instance, and the object compound can be obtained on elimination of such protective group after the reaction.

[0058] The protective group for the amino function includes optionally substituted C_{1-6} alkyl-carbonyl (e.g. formyl, acetyl, ethylcarbonyl, etc.), benzoyl, C_{1-6} alkyl-oxycarbonyl (e.g. methoxycarbonyl, ethoxycarbonyl), phenyloxycarbonyl (e.g. phenoxycarbonyl), C_{7-15} aralkyl-oxycarbonyl (e.g. benzyloxycarbonyl, fluorenyloxycarbonyl), trityl, phthaloyl and so on. The substituent group that may be present on these groups includes halogen (e.g. fluoro, chloro, bromo, iodo), C_{1-6} alkyl-carbonyl (e.g. methylcarbonyl, ethylcarbonyl, butylcarbonyl), nitro and so on. The number of substituents may range from 1 to 3.

[0059] The protective group that can be used for the hydroxyl function includes optionally substituted C_{1-6} alkyl (e.

g. methyl, ethyl, n-propyl, i-propyl, n-butyl, tert-butyl), phenyl, C_{7-10} aralkyl (e.g. benzyl), C_{1-6} alkyl-carbonyl (e.g. formyl, acetyl, ethylcarbonyl), phenyloxycarbonyl (e.g. phenoxycarbonyl), C_{7-10} aralkyl-carbonyl (e.g. benzyloxycarbonyl), pyranyl, furanyl, si-lyl and so on. The substituent group that may be present includes halogen (e.g. fluoro, chloro, bromo, iodo), C_{1-6} alkyl, phenyl, C_{7-10} aralkyl, nitro and so on. The number of substituents may range from 1 to 4.

[0060] The method of deprotection may be any per se known procedure or any procedure analogous thereto. For example, treatment with an acid or a base, reduction, irradiation with ultraviolet light, and treatment with hydrazine, phenylhydrazine, sodium N-methyldithiocarbamate, tetrabutylammonium fluoride, palladium acetate or the like can be mentioned.

[0061] When the compound (I) thus obtained is a free compound, it can be converted to a salt by the conventional procedure, while any salt thereof can be converted to the free compound or a different kind of salt by the procedure respectively known per se. The compound (I) or its salt thus obtained can be isolated and purified by the known procedures mentioned hereinbefore. While the compound (I) or its salt includes stereoisomers due to the presence of asymmetric carbon, these can also be isolated and purified by a choice of the above-mentioned known procedures, fractional recrystallization, chromatography on an optically active column, and other procedures.

[0062] The compound (I) and a salt thereof of this invention act on the central nervous system of mammalian animals and, having strong cholinesterase inhibitory activity, display excellent anti-amnesia activity against various amnestic factors in man and animals (e.g. mouse).

[0063] Furthermore, the compound (I) and salt thereof have monoamine (e.g. norepinephrine and serotonin)-reuptake inhibitory activity and exhibits excellent antidepressant effects in man and animals (e.g. mouse).

[0064] The compound (I), inclusive of its salt, is remarkably superior to physostigmine and THA in the isolation of central nervous system effect vs. peripheral nervous system effect and in doses producing antiamnesic and antidepressive effects, it causes no or little peripheral nervous symptoms such as convulsion, sialism and diarrhea, features a long duration of action and has a low toxic potential. It also exhibits remarkable efficacy on oral administration. The acute toxicity (LD_{50}) of the compound (I) or a salt thereof of this invention is not less than 100 mg/kg.

[0065] Therefore, the substance according to this invention is of value as a safe brain function-improving agent for man and other mammalian animals.

[0066] The disease in which the substance of this invention can be indicated with therapeutic success includes senile dementia, Altzheimer's disease, Huntigton's cholea, hyperkinesia and maniac and, therefore, the substance of this invention finds application in the prevention and treatment of these diseases.

[0067] The substance of this invention can be administered orally or otherwise, generally in admixture with a medicinally acceptable carrier or excepient, to mammals inclusive of man.

[0068] Such formulations may be provided in oral dosage forms (e.g. powders, tablets, granules, capsules) or parenteral dosage forms (e.g. suppositories, injections).

[0069] These dosage forms can be manufactured by the per se known methods. The dosage depends on the type and symptoms of the disease to be managed but generally speaking, about 0.01 mg-50 mg, preferably 0.1-30 mg, and more desirably 0.5-10 mg can be dispensed per day in the case of an adult (body weight: 70 kg).

[Examples]

[0070] The following examples, reference examples, formulation examples and test examples are all intended to illustrate this invention in further detail and should by no means be construed as defining the scope of the invention.

[0071] Unless otherwise indicated, all elution procedures in column chromatography as described in the test and reference examples were carried out under TLC (thin-layer chromatography) monitoring. In the TLC monitoring, Merck $60F_{254}$ was used as the TLC plate, the eluent for column chromatography was used as the TLC developer, and a UV detector was used for detection. In addition, the TLC plate was sprayed with 48% HBr, heated for hydrolysis, sprayed with ninhydrin reagent and reheated to see that the spot would turn red ~ red-purple. The fractions thus comfirmed to contain the object compound were pooled. Unless otherwise indicated, the column packing silica gel used was Merck's Kieselgel 60 (70-230 mesh).

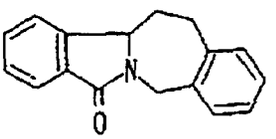
[0072] The term "atmospheric temperature" or "ambient temperature" as used herein generally means any temperature between about 5°C and about 40°C, while the term "atmospheric pressure" means any pressure in the neighborhood of 1 atm.

[0073] Unless otherwise indicated, % means a weight percentage and $C_4H_4O_4$ stands for fumaric acid.

Reference Example 1

7,11b,12,13-tetrahydro-5H-isoindro[2,1-b][2]benzazepin-7-one

[0074]



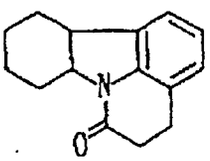
[0075] A mixture of 9.8 g 11b,12-dihydro-5H-isoindolo-[2,1-b][2,1-b]benzazepine-7,13-dione, 5.0 g potassium hydroxide, 4.3 ml hydrazine monohydrate and 50 ml ethylene glycol was heated at 120°C for 2 hours and, then, at 190°C for 3 hours. The reaction mixture was allowed to cool, after which it was diluted with water and extracted with dichloromethane. The extract was dried over anhydrous sodium sulfate and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (eluent: dichloromethane-ethyl acetate = 20 : 1 (v/v)) and the crystals obtained were recrystallized from ethyl acetate-ether to provide 4.2 g of the title compound as light-yellow needles melting at 170-171°C. Elemental analysis for $C_{17}H_{15}NO$

Calcd.: C, 81.90; H, 6.06; N, 5.62
Found : C, 81.76; H, 6.02; N, 5.48

Reference Example 2

2,3,6b,7,8,9,10,10a-Octahydro-1H-pyrido[3,2,1-jk]carbazol-1-one

[0076]



1) To a solution of 10 g 1,2,3,4,4a,9a-hexahydrocarbazole in 30 ml acetone was added a solution of 8.3 g 3-chloropropionyl chloride in 30 ml acetone dropwise at ambient temperature and the mixture was refluxed for 1 hour. The solvent was then distilled off under reduced pressure and the residue was dissolved in 100 ml of dichloromethane and washed with 10% hydrochloric acid twice. The solution was dried over anhydrous sodium sulfate and the solvent was distilled off under reduced pressure to provide about 17 g of 9-(3-chloropropionyl)-1,2,3,4,4a,9a-hexahydrocarbazole as a viscous oil. This oil was not purified but submitted directly to the next reaction.
2) The 9-(3-chloropropionyl)-1,2,3,4,4a,9a-hexahydrocarbazole (3.0 g) obtained as above was mixed with 3.3 g of anhydrous aluminum chloride and the mixture was heated at 120°C with stirring for 90 minutes. This mixture was diluted with iced water and extracted with dichloromethane. The extract was then washed with water and dried over anhydrous sodium sulfate and the solvent was distilled off. The residue was purified by silica gel column chromatography (eluent: ethyl acetate-dichloromethane = 1 : 1, v/v) to provide 1.7 g of the title compound as colorless crystals melting at 66-70°C.

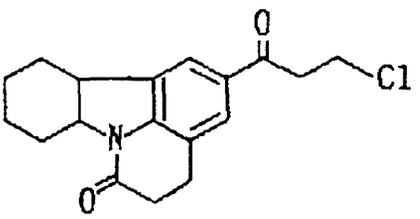
Elemental analysis for $C_{15}H_{17}NO$

Calcd.: C, 79.26; H, 7.54; N, 6.16
Found : C, 79.19; H, 7.52; N, 6.11

Reference Example 3

5-(3-Chloro-1-oxopropyl)-2,3,6b,7,8,9,10,10a-octahydro-1H-pyrido[3,2,1-jk]carbazol-1-one

[0077]



[0078] To a solution of 0.52 g 2,3,6b,7,8,9,10,10a-octahydro-lH-pyrido[3,2,1-jk]carbazol-1-one obtained in Reference Example 3 and 0.32 g 3-chloropropionyl chloride in 20 ml 1,2-dichloroethane was added 0.70 g of anhydrous aluminum chloride portionwise and the mixture was refluxed for 1 hour. The reaction mixture was allowed to cool, poured in iced water and extracted with dichloromethane. The extract was washed with water and dried over anhydrous sodium sulfate and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (eluent: ethyl acetate-dichloromethane = 1 : 1, v/v) to provide 0.50 g of the title compound as colorless crystals melting at 126-128°C.
Elemental analysis for $C_{18}H_{20}ClNO_2$

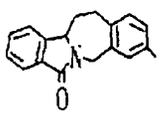
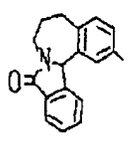
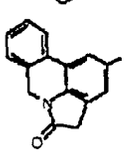
Calcd.: C, 68.03; H, 6.34; N, 4.41
Found : C, 67.81; H, 6.37; N, 4.39

Reference Example 4

[0079] Using the compound obtained in Reference Example 1 or a known tetracyclic fused ring and 3-chloropropionyl chloride, the procedure of Reference Example 3 was otherwise repeated to provide the compounds shown in Table 13.

[Table 13]

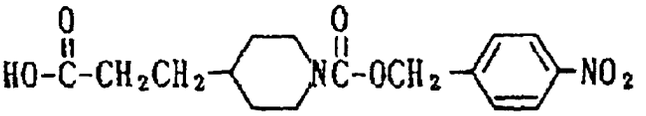
$Ar-\overset{\overset{O}{\|}}{C}-CH_2CH_2Cl$

Compound No.	Ar	Melting Point (℃)	Molecular formula	Elemental analysis Calcd.(Found) C	H	N
1		139-142	$C_{20}H_{18}ClNO_2$	70.69	5.34	4.12
				(70.72	5.39	4.10)
2		152-156	$C_{20}H_{18}ClNO_2$	70.69	5.34	4.12
				(70.61	5.39	4.13)
3		92-95	$C_{18}H_{14}NO_2Cl$	69.35	4.53	4.49
				(69.11	4.75	4.27)

Reference Example 5

3-[1-[(4-Nitrophenyl)methoxycarbonyl]-4-piperidinyl]propionic acid

[0080]



[0081] A mixture of 20.0 g 3-(1-acetyl-4-piperidinyl)-propionic acid and 40 ml concentrated hydrochloric acid was refluxed for 14 hours. The hydrochloric acid was then distilled off under reduced pressure and the residual powder was washed with ether and dried under reduced pressure to provide 19.0 g of a colorless powder. To a solution of this powder in 170 ml 1N-sodium hydroxide solution was added a solution of 12.2 g p-nitrobenzyl chloroformate in 60 ml dichloromethane with ice cooling and the mixture was then stirred vigorously at ambient temperature for 1 hour. The organic layer was separated from this reaction mixture and the aqueous layer was acidified with 3N-hydrochloric acid and extracted with dichloromethane. The extract was dried over anhydrous sodium sulfate and the solvent was distilled off under reduced pressure. The residue was dissolved in dichloromethane with heating and ether was then added. The mixture was allowed to cool and the resulting powder was collected by filtration and dried under reduced pressure to provide 16.6 g of the title compound as a colorless powder melting at 98-99°C.
Elemental analysis for $C_{16}H_{20}N_2O_6$

Calcd.: C, 57.14; H, 5.99; N, 8.33
Found : C, 57.05; H, 6.01; N, 8.28

Reference Example 6

4,5-Dihydro-7H-pyrrolo[3,2,1-de]phenanthridin-4-one

[0082]

a) 5-(Chloroacetyl)-4,5-dihydrophenanthridine

A solution of chloroacetyl chloride (17 g) in dichloromethane (20 ml) was added dropwise to a mixture of 5,6-dihydrophenanthridine (25 g) in dichloromethane (80 ml) and 1N-NaOH with vigorous stirring at 0°C. The mixture was allowed to warm to room temperature and stirring was continued for an hour. An organic phase was separated, washed with sat. $NaHCO_3$ twice, dried over Na_2SO_4 and concentrated in vacuo. The resulting solid was recrystallized from ethyl acetate-hexane to give 33 g of the title compound as colorless needles, mp 115-117°C. Anal. Calcd for $C_{15}H_{12}NOCl$: C, 69.91; H, 4.69; N, 5.43. Found: C, 69.85; H, 4.41; N, 5.33.

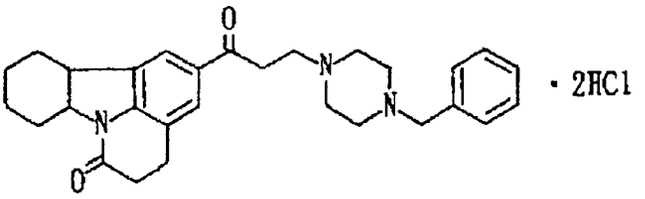
b) 4,5-Dihydro-7H-pyrrolo[3,2,1-de]phenanthridin-4-one

A mixutre of 5-(chloroacetyl)-4,5-dihydrophenanthridine (30 g) and aluminum chloride (36 g) was warmed up to 140°C and stirred for 10 minutes. Water was added to the mixture and extracted with dichloromethane. The extracts were washed with water, dried over Na_2SO_4 and concentrated in vacuo. The resulting solid was recrystallized from dichloromethane-ether to give 18 g of the title compound as colorless needles, mp 199-202°C. Anal. Calcd for $C_{15}H_{11}NO$: C, 81.43; H, 5.01; N, 6.33. Found: C, 81.16; H, 5.18; N, 6.29.

Example 1

5-[3-[4-(Phenylmethyl)-1-piperazinyl]-1-oxopropyl]-2,3,6b,7,8,9,10,10a-octahydro-1H-pyrido[3,2,1-jk]carbazol-1-one dihydrochloride

[0083]



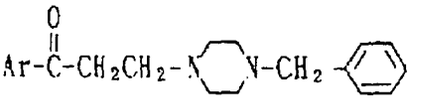
[0084] A mixture of 0.40 g 5-(3-chloro-1-oxopropyl)-2,3,6b,7,8,9,10,10a-octahydro-1H-pyrido[3,2,1-jk]-carbazol-1-one as obtained in Reference Example 3, 0.23 g potassium carbonate, 0.29 g 1-benzylpiperazine and 20 ml dichloromethane-methanol (1 : 1, v/v) was stirred at ambient temperature for 14 hours and the solvent was then distilled off under reduced pressure. The residue was diluted with water and extracted with dichloromethane. The extract was washed with water, dried over anhydrous sodium sulfate and the solvent was distilled off. The risidue was purified by silica gel column chromatography (eluent: ethyl acetate-methanol = 4 : 1, v/v) to provide 0.61 g of the free base form of the title compound as oil. This oil was dissilved in methanol followed by addition of 0.8 ml of 4N-methanolic HCl. The resulting crystals were collected by filtration, washed with ether and dried under reduced pressure to provide 0.59 g of the title compound as colorless crystals melting at 199-203°C (decomp.).
Elemental analysis for $C_{29}H_{35}N_3O_2$•2HCl•H_2O

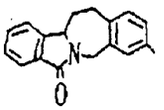
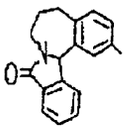
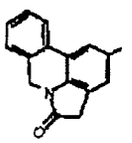
Calcd.: C, 63.50; H, 7.17; N, 7.66
Found : C, 63.22; H, 7.10; N, 7.73

Example 2

[0085] Using the compound obtained in Reference Example 4, the procedure of Example 1 was otherwise repeated to provide the compounds shown in Table 14.

[Table 14]

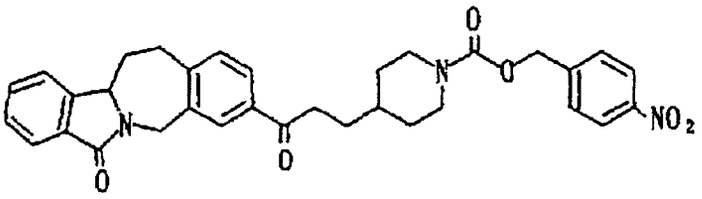


Compound No.	Ar	Melting point (°C)	Molecular formula	Elemental analysis Calcd. (Found) C	H	N
1		195-197	$C_{31}H_{33}N_3O_2 \cdot 2HCl \cdot H_2O$	65.26 (65.52)	6.54 (6.43)	7.36 (7.30)
2		147-152	$C_{31}H_{33}N_3O_2 \cdot 2HCl \cdot 2H_2O$	63.26 (63.47)	6.68 (6.94)	7.14 (6.80)
3		222-225 (decomposition)	$C_{29}H_{29}N_3O_2 \cdot 2HCl \cdot 2H_2O$	64.21 (64.35)	6.13 (6.08)	7.75 (7.81)

Reference Example 7

3-[3-[1-[(4-Nitrophenyl)methoxycarbony]-4-piperidinyl]-1-oxo-propyl]-7,11b,12,13-tetrahydro-5H-isoindolo[2,1-b][2]benzazepin-7-one

[0086]



[0087] 3-[1-[(4-Nitrophenyl)methoxycarbonyl]-4-piperidinyl]propionic acid as obtained in Reference Example 6 (2.45 g) was added to 10 ml of thionyl chloride at 0-5°C and the mixture was stirred at 0-5°C for 20 minutes. The excess thionyl chloride was then distilled off under reduced pressure. This residue and 1.6 g of the 7,11b,12,13-tetrahydro-5H-isoindolo[2,1-b]-[2]benzazepin-7-one obtained in Reference Example 1 were dissolved in 30 ml of 1,2-dichloroethane and 3.0 g of anhydrous aluminum chloride was added in small portions to the solution. The mixture was stirred at ambient temperature for 14 hours. The reaction mixture was then poured in iced water and extracted with dichloromethane. The extract was washed with water and dried over anhydrous sodium sulfate and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (eluent: dichloromethane-ethyl acetate = 20 : 1, v/v) to provide 0.90 g of the title compound as colorless crystals melting at 179-181°C.

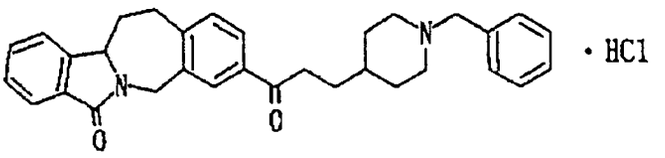
Elemental analysis for $C_{33}H_{33}N_3O_6$

Calcd.: C, 69.83; H, 5.86; N, 7.40
Found : C, 69.69; H, 5.73; N, 7.38

Example 3

3-[3-[1-(Phenylmethyl)-4-piperidinyl]-1-oxopropyl]-7,11b,12,13-tetrahydro-5H-isoindolo[2,1-b][2]benzazepin-7-one hydrochloride

[0088]



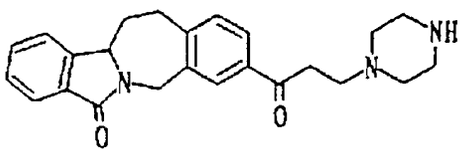
[0089] A solution of 0.8 g 3-[3-[1-[(4-nitrophenyl)-methoxycarbonyl]-4-piperidinyl]-1-oxopropyl]-7,11b,12,13-tetrahydro-5H-isoindolo[2,1-b][2]-benzazepin-7-one as obtained in Reference Example 7 in 40 ml methanol was mixed with 0.4 ml 4N-methanolic HCl and the mixture was subjected to catalytic hydrogenation reaction in the presence of 10% Pd/C at atmospheric pressure. After completion of the reaction, the 10% Pd/C was filtered off and the filtrate was concentrated. The residue was dissolved in water, adjusted to pH 10-11 with 10% aqueous sodium hydroxide solution and extracted with dichloromethane. The extract was washed with water and dried over anhydrous sodium sulfate and the solvent was distilled off under reduced pressure to recover 0.53 g of oil. To a suspension comprising 0.43 g of this oil, 0.2 g of potassium carbonate and 10 ml of ethanol was added a solution of 0.18 g benzyl bromide in 2 ml ethanol dropwise and the mixture was stirred at ambient temperature for 4 hours. The solvent was then distilled off under reduced pressure and the residue was dissolved in water and extracted with dichloromethane. The extract was washed with water and dried over anhydrous sodium sulfate and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (eluent: ethyl acetate-methanol = 40 : 1, v/v) to provide 0.36 g of the free base form of the title compound as a colorless powder melting at 146-147°C. This powder was dissolved in methanol followed by addition of 0.3 ml of 4N-methanolic HCl. After the solvent was distilled off, isopropyl alcohol was added and the resulting solid was dried under reduced pressure to provide 0.35 g of the title compound as a colorless powder melting at 179-181°C.
Elemental analysis for $C_{32}H_{34}N_2O_2 \cdot HCl \cdot 1/2H_2O$

Calcd.: C, 73.34; H, 6.92; N, 5.35
Found : C, 73.56; H, 6.90; N, 5.25

Reference Example 8

3-[1-Oxo-3-(1-piperazinyl)propyl]-7,11b,12,13-tetrahydro-5H-isoindolo[2,1-b][2]benzazepin-7-one

[0090]



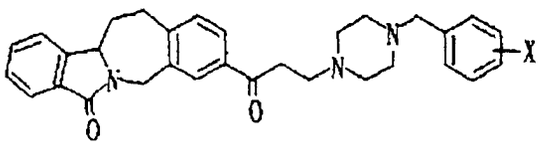
[0091] Using 3.45 g of 3-(3-chloro-1-oxopropyl)-7,11b,12,13-tetrahydro-5H-isoindolo[2,1-b][2]benzazepin-7-one, corresponding to Reference Example 4 Compound No. 1, and 1.4 g of 1-formylpiperazine, the procedure of Example 1 was otherwise repeated to provide about 3.6 g of 3-[3-(4-formyl-1-piperazinyl)-1-oxopropyl]-7,11b,12,13-te-trahydro-5H-isoindolo[2,1-b][2]benzazepin-7-one as a crude oil. This oil was not further purified but directly dissolved in 50 ml of methanol and the solution was refluxed with 50 ml of concentrated hydrochloric acid for 4 hours. After the methanol was distilled off, the residual aqueous solution was adjusted to pH about 10 with 10% aqueous sodium hydroxide solution and the product was extracted into dichloromethane. The extract was washed with water and the solvent was distilled off under reduced pressure to provide 3.1 g of the title compound as a powder melting at 207-210°C.
Elemental analysis for $C_{24}H_{27}N_3O_2$

Calcd.: C, 74.01; H, 6.99; N, 10.79
Found : C, 73.92; H, 7.05; N, 11.84

Example 4

[0092] Using the compound obtained in Reference Example 8 and various kinds of substituted benzyl bromide, the procedure of Example 1 was repeated to provide the compounds shown in Table 15.

[Table 15]

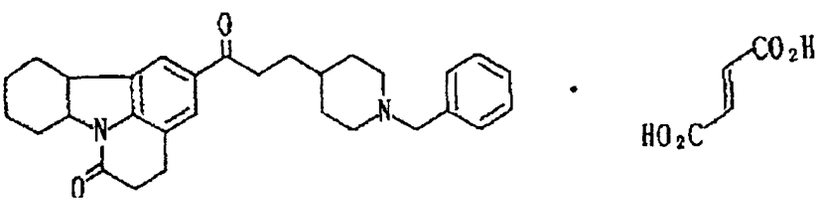


Compound No.	X	Melting point (℃)	Molecular formula	Elemental analysis Calcd.(Found) C	H	N
1	3-CH_3	207-211 (decomp.)	$C_{32}H_{35}N_3O_2\cdot 2HCl\cdot 5/2H_2O$	62.84 (62.91	6.92 6.98	6.87 6.92)
2	3-Cl	206-208 (decomp.)	$C_{31}H_{32}ClN_3O_2\cdot 2HCl\cdot 1/2H_2O$	62.47 (62.54	5.92 5.84	7.05 6.95)
3	3-F	194-196 (decomp.)	$C_{31}H_{32}FN_3O_2\cdot 2HCl\cdot 1/2H_2O$	64.25 (64.44	6.09 5.99	7.25 7.01)
4	3-CN	199-202 (decomp.)	$C_{32}H_{32}N_4O_2\cdot 2HCl\cdot 1/2H_2O$	65.53 (65.13	6.01 5.76	9.55 9.24)

Example 5

5-[3-[1-(Phenylmethyl)-4-piperidinyl]-1-oxopropyl]-2,3,6b,7,8,9,10,10a-octahydro-1H-pyrido[3,2,1-jk]carbazol-1-one fumarate

[0093]



1) One (1.0) gram of 3-(1-methoxycarbonyl-4-piperidinyl)propionic acid was added to 5 ml of thionyl chloride at 0-5°C and the mixture was stirred at 0-5°C for 20 minutes. The excess thionyl chloride was distilled off under reduced pressure. To a solution of this distillation residue and 1.0 g 2,3,6b,7,8,9,10,10a-octahydro-1H-pyrido

[3,2,1-jk]carbazol-1-one as obtained in Reference Example 2 in 50 ml 1,2-dichloroethane was added 2.1 g of anhydrous aluminum chloride portionwise and the mixture was stirred at ambient temperature for 14 hours. The reaction mixture was poured in iced water and extracted with dichloromethane. The extract was washed with 10 % aqueous sodium hydroxide solution and water in that order and dried over anhydrous sodium sulfate and the solvent was then distilled off under reduced pressure. The residue was purified by silica gel column chromatography (eluent: dichloromethane-ethyl acetate = 10 : 1, v/v) to provide 0.69 g of 5-[3-[1-(methoxycarbonyl)-4-piperidinyl]-1-oxopropyl]-2,3,6b,7,8,9,10,10a-octahydro-1H-pyrido[3,2,1-jk]carbazol-1-one. In addition, 0.34 g of the starting compound 2,3,6b,7,8,9,10,10a-octahydro-1H-pyrido[3,2,1-jk]carbazol-1-one was recovered.

2) A mixture of 0.38 g of the compound obtained in 1) above and 20 ml of concentrated hydrochloric acid was refluxed for 14 hours. The hydrochloric acid was then distilled off under reduced pressure and the residue was diluted with water and washed with ethyl acetate. This aqueous solution was adjusted to pH about 10 with 10% aqueous sodium hydroxide solution and extracted with dichloromethane. The extract was washed with water and dried over anhydrous sodium sulfate and the solvent was distilled off under reduced pressure. To a suspension comprising 0.27 g of the oily residue, 0.13 g of potassium carbonate and 15 ml of methanol was added a solution of 0.115 g benzyl bromide in 3 ml methanol and the mixture was stirred at ambient temperature for 4 hours. The solvent was then distilled off and the residue was diluted with water and extracted with dichloromethane. This extract was washed with water and dried over anhydrous sodium sulfate and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (eluent: ethyl acetate-methanol = 10 : 1, v/v) to provide 0.2 g of the free base form of the title compound as oil. This oil was treated with 1 equivalent of fumaric acid to provide 0.2 g of the title compound as a colorless amorphous powder.

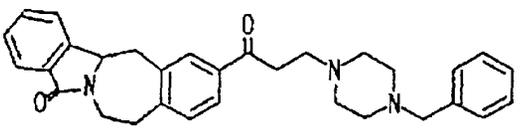
Elemental analysis for $C_{30}H_{36}N_2O_2 \cdot C_4H_4O_4 \cdot 2H_2O$

Calcd.: C, 67.09; H, 7.29; N, 4.60
Found : C, 67.29; H, 6.97; N, 4.32

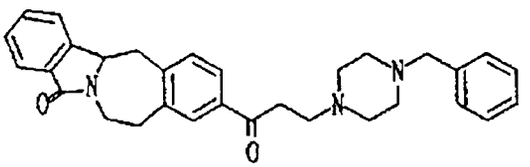
Example 6

11-[1-Oxo-3-[4-(phenylmethyl)-1-piperazinyl]]-7,8,13,13a-tetrahydro-5H-isoindolo[1,2-b][3]benzazepin-5-one dihydrochloride(A) and 10-[1-oxo-3-[4-(phenylmethyl)-l-piperazinyl]]-7,8,13,13a-tetrahydro-5H-isoindolo[1,2-b][3] benzazepin-5-one dihydrochloride(B)

[0094]



· 2HCl (A)



· 2HCl (B)

[0095] To a solution of 2.49 g 7,8,13,13a-tetrahydro-5H-isoindolo[l,2-b][3]benzazepin-one and 1.05 ml 3-chloropropionyl chloride in 25 ml 1,2-dichloroethane was added 2.93 g of anhydrous aluminum chloride portionwise and the mixture was stirred at ambient temperature for 3 hours. The reaction mixture was poured in iced water and extracted with dichloromethane. This extract was washed with iN-aqueous sodium hydroxide solution and water in the order mentioned and dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure and the residue was purified by silica gel column chromatography (eluent: dichloromethane-ethyl acetate = 10 : 1, v/v) to give 2.46 g of a light-yellow powder. To a suspension comprising 1.70 g of the above powder, 0.69 g of potassium carbonate and 43 ml of ethanol was added 1.04 ml of 1-benzylpiperazine and the mixture was stirred at ambient temperature for 5 hours. The solvent was then distilled off under reduced pressure and the residue was diluted with water and extracted

with dichloromethane. This extract was washed with water and dried over anhydrous sodium sulfate and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (eluent: ethyl acetate-methanol = 10 : 1, v/v) to provide 2.20 g of the free base forms of the title compound as a colorless powder. This powder (0.96 g) was treated with methanolic hydrochloric acid (2 equivalents) to provide 0.76 g of an approximately 4 : 1 mixture of the title compounds (A) and (B) as an amorphous powder.
Elemental analysis for $C_{31}H_{33}N_3O_2$•2HCl•1/2H_2O

Calcd.: C, 66.31; H, 6.46; N, 7.48
Found : C, 66.20; H, 6.52; N, 7.42

Formulation Example 1

[0096]

(1) 3-[3-[1-(Phenylmethyl)-4-piperidinyl]-1-oxopropyl]-7,11b,12,13-tetrahydro-5H-isoindolo[2,1-b][2]benzazepin-7-one hydrochloride (the compound of Example 3) 1 g
(2) Lactose 197 g
(3) Corn starch 50 g
(4) Magnesium stearate 2 g

[0097] One gram of (1), 197 g of (2) and 20 g of (3) (corn starch) were blended and granulated together with a paste prepared from 15 g of corn starch and 25 ml of water. To this granuation was added 15 g of corn starch and 2 g of (4) and the composition was compressed with a tablet machine to manufacture 2000 tablets each containing 0.5 mg of (1) and measuring 3 mm in diameter.

Formulation Example 2

[0098]

(1) 3-[3-[1-(Phenylmethyl)-4-piperidinyl]-1-oxopropyl]-7,11b,12,13-tetrahydro-5H-isoindolo[2,1-b][2]benzazepin-7-one hydrochloride (the compound of Example 3) 2 g
(2) Lactose 197 g
(3) Corn starch 50 g
(4) Magnesium stearate 2 g

[0099] Two grams of (1), 197 g of (2) and 20 g of (3) (corn starch) were blended and granulated together with a paste prepared from 15 g of corn starch and 25 ml of water. To this granulation was added 15 g of corn starch and 2 g of (4) and the composition was compressed with a tablet machine to manufacture 2000 tablets each measuring 3 mm in diameter and containing 1.0 mg of (1).

[Test Example 1]

[0100] The cholinesterase inhibitory activity of the compound of this invention was evaluated using (acetyl-[^{3}H])-acetylcholine. Thus, using the S_1 fraction of a male Wistar rat cerebral cortex homogenate as a source of cholinesterase, (acetyl[^{3}H])-acetylcholine as a substrate, and the compound of this invention as a test substance, the system was incubated for 30 minutes. The reaction was then stopped and a toluenic scincillator was added. After shaking, [^{3}H]-acetic acid produced and transferred into the toluene layer was counted with a liquid scincillation counter to estimate the cholinesterase inhibitory activity of the test substance.
[0101] The cholinesterase inhibitory activity of the test compound was expressed in 50 % inhibitory concentration (IC_{50}). The cholinesterase inhibitory activity values of physostigmine and THA were also determined in a similar fashion.
[0102] The data are presented in Table 16.

[Table 16]

Compound (Example No.)	Acetylcholinesterase inhibitory activity IC_{50} (μM)
1	0.0775
2-1	0.0164

[Table 16] (continued)

Compound (Example No.)	Acetylcholinesterase inhibitory activity IC_{50} (μM)
3	0.0024
4 - 2	0.0655
4 - 3	0.0174
5	0.00793
6	0.00403
Physostigmine	0.220
THA	0.300

[0103] It is apparent from Table 16 that the compound of this invention is superior to physostigmine and THA in acetylcholinesterase inhibitory activity.

[Test Example 2]

[0104] The monoamine reuptake inhibitory activity of the compound of this invention was evaluated using [^{3}H]-norepinephrine (NE) and [^{3}H]-serotonin(5-HT).

[0105] Thus, the brain was enuleated from male JC1: Wistar rats (aged 9-13 weeks) and the cerebral cortex and the hippocampus were isolated. The tissue was homogenized (Potter, 5 strokes) with about 10-15 volumes of ice-cooled 0.32 M sucrose and centrifuged at 1.000 x g for 10 minutes. The supernatant was further centrifuged at 20,000 x g for 20 minutes to provide a pellet (P_2). This pellet was suspended in Krebs-Ringer bicarbonate solution (KRB) (KRB: 116 mM NaCl, 4.8 mM KCl, 1.3 mM $CaCl_2$, 1,2 mM $MgSO_4$, 1,2 mM NaH_2PO_4, 25 mM $NaHCO_3$, 0.1 mM EDTA-2Na, 11.1 mM D-glucose, 0.11 mM L-ascorbic acid, 0.01 mM pargyline-HCl; 95 % O_2/5 % CO_2) and aliquots of the suspension were used for assays.

[0106] The test compound (10 μl as dissolved in DMSO at 100 times the final concentration) was mixed with 900 μl of the P_2 suspension and the mixture was preincubated at 37°C for 5 minutes. Then, 100 μl of [^{3}H]-NE (final concentration 11 nM) or [^{3}H]-5-HT (final concentration 10 nM) was added and the mixture was incubated at 37°C for 5 minutes. After addition of 4 ml ice-cooled KRB to the assay tube, the mixture was immediately filtered through a Whatman CF/B filter under reduced pressure, and the filter was further washed with 4 ml of KRB twice. The filter was transferred to a minature vial, 4 ml of scintillator was added, and the radioactivity was counted with a liquid scintillation counter.

[0107] As a control drug, imipramine was used. The test compound was invariably tested at 4 final concentrations of 10^{-8}, 10^{-7}, 10^{-6}, and 10^{-5} M.

[0108] The data are presented in Table 17.

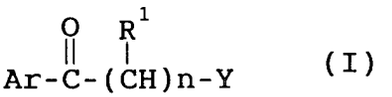
[Table 17]

Example No.	Monoamine uptake inhibitory activity IC_{50} (μM)	
(Compound No.)	NE	5-HT
2-1	1.04	0.070
Imipramine	1.12	0.063

[0109] It is apparent from Table 17 that the compound of this invention is as potent as the control drug imipramine in monoamine uptake inhibitory activity.

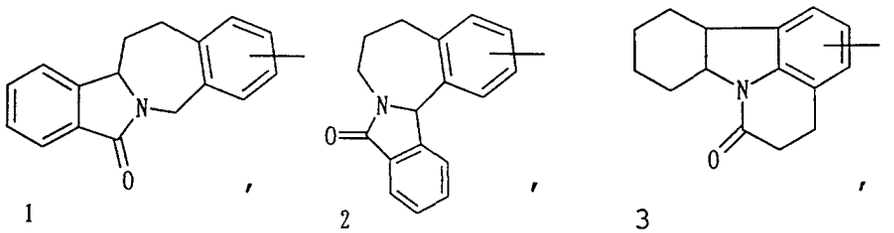
Claims

1. A compound of the formula:

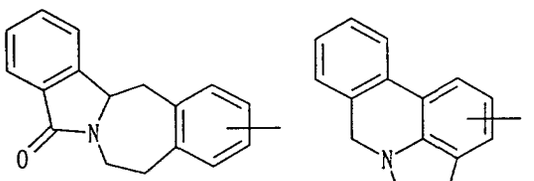


$$Ar\text{-}C(=O)\text{-}(CH)n\text{-}Y \quad (I)$$

wherein Ar represents a group of the formula:



1 , 2 , 3 ,



4 or 5

n represents an integer of 1 to 10;
R^1 represents a hydrogen atom; and
Y represents a 1- or 4-piperidinyl or 1-piperazinyl group substituted by a benzyl which may be substituted by halogen, C_{1-4} alkyl, C_{1-4} alkoxy, hydroxy, nitro, amino or cyano; or a salt thereof.

2. The compound according to claim 1, wherein Ar is 7-oxo-7,11b,12,13-tetrahydro-5H-isoindolo[2,1-b][2]-benzazepin-3-yl.

3. The compound according to claim 1, wherein Ar is 1-oxo-2,3,6b,7,8,9,10,10a-octahydro-1H-pyrido[3,2,1-jk]carbazol-5-yl.

4. The compound according to claim 1, wherein Ar is 9-oxo-6,7,9,13b-tetrahydro-5H-isoindolo[1,2-a][2]-benzazepin-2-yl.

5. The compound according to claim 1, wherein Ar is 5-oxo-7,8,13,13a-tetrahydro-5H-isoindolo[1,2-b][3]benzazepin-10 or 11-yl.

6. The compound according to claim 1, which is 1-(7-oxo-7,11b,12b,13-tetrahydro-5H-isoindolo[2,1-b][2]benzazepin-3-yl)-3-[4-(phenylmethyl)-1-piperazinyl]-1-propanone or a salt thereof.

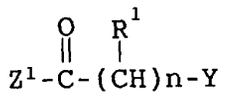
7. The compound according to claim 1, which is 1-(9-oxo-6,7,9,13b-tetrahydro-5H-isoindolo[1,2-a][2]benzazepin-2-yl-3-[4-(phenylmethyl)-1-piperazinyl]-1-propanone or a salt thereof.

8. A process for producing a compound of claim 1 which comprises

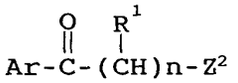
i) reacting a compound of the formula:

Ar-H

wherein Ar has the same meaning as defined in claim 1 or a salt thereof with a compound of the formula:



wherein Z^1 represents a leaving group and the other symbols have the same meanings as defined in claim 1 or a salt thereof; or
ii) reacting a compound of the formula:



wherein Z^2 represents a leaving group and the other symbols have the same meanings as defined in claim 1 or a salt thereof with a compound of the formula:

$$Z^3\text{-}Y$$

wherein Z^3 represents a leaving group and Y has the same meaning as defined in claim 1 or a salt thereof.

9. A cholinesterase inhibitory composition which contains an effective cholinesterase inhibiting amount of a compound of the formula (I) as claimed in claim 1 or a pharmaceutically acceptable salt thereof and a pharmacologically acceptable carrier.

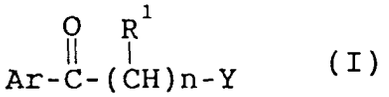
10. A cholinesterase inhibitory composition for treating a disease caused by cholinesterase activity, which contains an effective cholinesterase inhibiting amount of a compound of the formula (I) as claimed in claim 1 or a pharmaceutically acceptable salt thereof and a pharmacologically acceptable carrier.

11. A pharmaceutical composition as claimed in claim 10 in which the disease is senile dementia and/or Alzheimer's disease.

12. Use of a compound of the formula (I) as claimed in claim 1 or a pharmaceutically acceptable salt thereof, as a component in the preparation of a cholinesterase inhibitor.

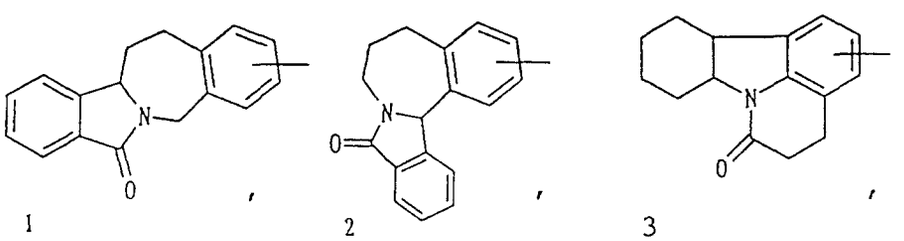
Patentansprüche

1. Verbindung der Formel

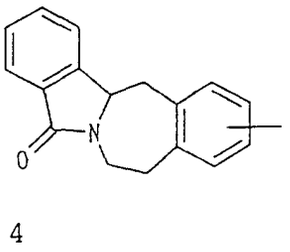


(I)

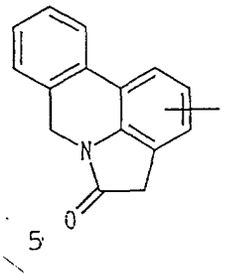
wobei Ar eine Gruppe der Formel



1 , 2 , 3 ,



oder



darstellt;

n eine ganze Zahl von 1 bis 10 darstellt;

R^1 ein Wasserstoffatom darstellt; und

Y eine 1- oder 4-Piperidinyl- oder 1-Piperazinylgruppe darstellt, die mit einem Benzyl substituiert ist, das mit Halogen, C_{1-4}-Alkyl, C_{1-4}-Alkoxy, Hydroxy, Nitro, Amino oder Cyan substituiert sein kann;

oder ein Salz davon.

2. Verbindung gemäß Anspruch 1, wobei Ar 7-Oxo-7,11b,12,13-tetrahydro-5H-isoindolo[2,1-b][2]benzazepin-3-yl ist.

3. Verbindung gemäß Anspruch 1, wobei Ar 1-Oxo-2,3,6b,7,8,9,10,10a-octahydro-lH-pyrido[3,2,1-jk]carbazol-5-yl ist.

4. Verbindung gemäß Anspruch 1, wobei Ar 9-Oxo-6,7,9,13b-tetrahydro-5H-isoindolo[1,2-a][2]benzazepin-2-yl ist.

5. Verbindung gemäß Anspruch 1, wobei Ar 5-Oxo-7,8,13,13a-tetrahydro-5H-isoindolo[1,2-b][3]benzazepin-10- oder -11-yl ist.

6. Verbindung gemäß Anspruch 1, bei der es sich um 1-(7-Oxo-7,11b,12b,13-tetrahydro-5H-isoindolo[2,1-b][2]benzazepin-3-yl)-3-[4-(phenylmethyl)-1-piperazinyl]-1-propanon oder ein Salz davon handelt.

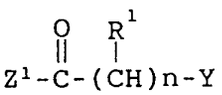
7. Verbindung gemäß Anspruch 1, bei der es sich um 1-(9-Oxo-6,7,9,13b-tetrahydro-5H-isoindolo[1,2-a][2]benzazepin-2-yl)-3-[4-(phenylmethyl)-1-piperazinyl]-1-propanon oder ein Salz davon handelt.

8. Verfahren zur Herstellung einer Verbindung gemäß Anspruch 1, das folgendes umfasst:

i) Umsetzen einer Verbindung der Formel

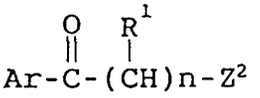
Ar-H,

wobei Ar dasselbe wie in Anspruch 1 bedeutet, oder eines Salzes davon mit einer Verbindung der Formel



wobei Z^1 eine Abgangsgruppe darstellt und die anderen Symbole dasselbe wie in Anspruch 1 bedeuten, oder einem Salz davon; oder

ii) Umsetzen einer Verbindung der Formel



wobei Z^2 eine Abgangsgruppe darstellt und die anderen Symbole dasselbe wie in Anspruch 1 bedeuten, oder eines Salzes davon mit einer Verbindung der Formel

$$Z^3\text{-}Y$$

wobei Z^3 eine Abgangsgruppe darstellt und Y dasselbe wie in Anspruch 1 bedeutet, oder einem Salz davon.

9. Cholin-Esterase-hemmende Zusammensetzung, die eine wirksame Cholin-Esterase-hemmende Menge einer Verbindung der Formel (I), wie sie in Anspruch 1 definiert ist, oder eines pharmazeutisch annehmbaren Salzes davon sowie einen pharmakologisch annehmbaren Träger enthält.

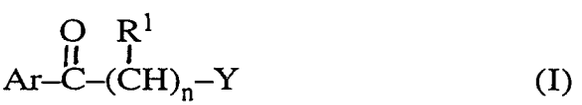
10. Cholin-Esterase-hemmende Zusammensetzung zur Behandlung einer durch Choiin-Esterase-Aktivität verursachten Krankheit, die eine wirksame Cholin-Esterase-hemmende Menge einer Verbindung der Formel (I), wie sie in Anspruch 1 definiert ist, oder eines pharmazeutisch annehmbaren Salzes davon sowie einen pharmakologisch annehmbaren Träger enthält.

11. Pharmazeutische Zusammensetzung gemäß Anspruch 10, wobei es sich bei der Krankheit um senile Demenz und/oder Alzheimer-Krankheit handelt.

12. Verwendung einer Verbindung der Formel (I), wie sie in Anspruch 1 definiert ist, oder eines pharmazeutisch annehmbaren Salzes davon als Komponente bei der Herstellung eines Cholin-Esterase-Inhibitors.

Revendications

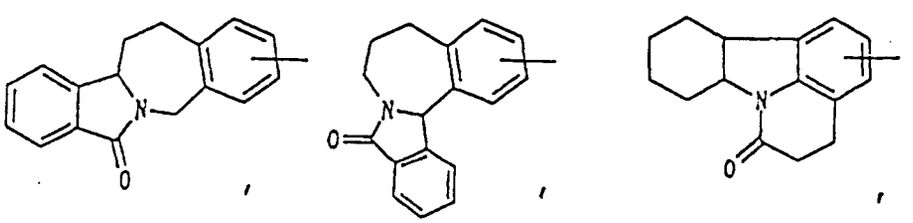
1. Composé de formule



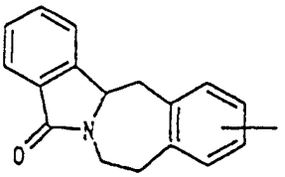
(I)

dans laquelle

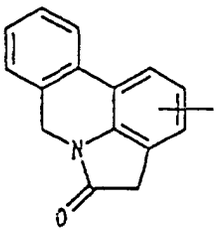
Ar représente un groupe de formule



1 2 3



4 ou



5

n représente un nombre entier valant de 1 à 10,
R^1 représente un atome d'hydrogène, et
Y représente un groupe 1-pipéridinyle, 4-pipéridinyle ou 1-pipérazinyle, portant un substituant benzyle qui peut lui-même porter un ou des substituants halogéno, alkyle en C_{1-4}, alcoxy en C_{1-4}, hydroxy, nitro, amino ou cyano ;

ou sel d'un tel composé.

2. Composé conforme à la revendication 1, dans lequel Ar représente un groupe 7-oxo-7,11b,12,13-tétrahydro-5H-isoindolo[2,1-b]-[2]benzazépin-3-yle.

3. Composé conforme à la revendication 1, dans lequel Ar représente un groupe 1-oxo-2,3,6b,7,8,9,10,10a-octahydro-1H-pyrido-[3,2,1-jk]carbazol-5-yle.

4. Composé conforme à la revendication 1, dans lequel Ar représente un groupe 9-oxo-6,7,9,13b-tétrahydro-5H-isoindolo[1,2-a]-[2] benzazépin-2-yle.

5. Composé conforme à la revendication 1, dans lequel Ar représente un groupe 5-oxo-7,8,13,13a-tétrahydro-5H-isoindolo[1,2-b]-[3]benzazépin-10- ou -11-yle.

6. Composé conforme à la revendication 1, qui est la 1-(7-oxo-7,11b,12b,13-tétrahydro-5H-isoindolo[2,1-b][2]benzazépin-3-yl)-3-[4-(phénylméthyl)-1-pipérazinyl]-1-propanone, ou l'un de ses sels.

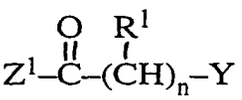
7. Composé conforme à la revendication 1, qui est la 1-(9-oxo-6,7,9,13b-tétrahydro-5H-isoindolo[1,2-a][2]benzazépin-2-yl)-3-[4-(phénylméthyl)-1-pipérazinyl]-1-propanone, ou l'un de ses sels.

8. Procédé de préparation d'un composé conforme à la revendication 1, qui comporte

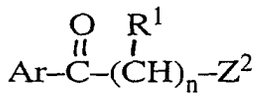
1) le fait de faire réagir un composé de formule

Ar-H

dans laquelle Ar a la même signification que celle indiquée dans la revendication 1,
ou un sel d'un tel composé, avec un composé de formule



dans laquelle Z^1 représente un groupe partant et les autres symboles ont les mêmes significations que celles indiquées dans la revendication 1,
ou avec un sel d'un tel composé ; ou bien
2) le fait de faire réagir un composé de formule



dans laquelle Z^2 représente un groupe partant et les autres symboles ont les mêmes significations que celles indiquées dans la revendication 1,
ou un sel d'un tel composé, avec un composé de formule

dans laquelle Z^3 représente un groupe partant et Y a la même signification que celle indiquée dans la revendication 1,
ou avec un sel d'un tel composé.

9. Composition inhibant la cholinestérase, qui contient un composé de formule (I) conforme à la revendication 1 ou un sel admissible en pharmacie d'un tel composé, en une quantité suffisante pour inhiber effectivement la cholinestérase, et un véhicule admissible en pharmacie.

10. Composition inhibant la cholinestérase et destinée au traitement d'une maladie provoquée par l'activité de la cholinestérase, qui contient un composé de formule (I) conforme à la revendication 1 ou un sel admissible en pharmacie d'un tel composé, en une quantité suffisante pour inhiber effectivement la cholinestérase, et un véhicule admissible en pharmacie.

11. Composition pharmaceutique conforme à la revendication 10, ladite maladie étant la démence sénile et/ou la maladie d'Alzheimer.

12. Emploi d'un composé de formule (I), conforme à la revendication 1, ou d'un sel admissible en pharmacie d'un tel composé, en tant que composant dans la préparation d'un inhibiteur de la cholinestérase.